

REMARKS

The Examiner's time and attention during an interview conducted May 27, 2009 are acknowledged and appreciated. Also present at the interview were Thomas Lundqvist (Executive Vice President and Head of Pharmaceutical and Clinical Research and Development, Orexo AB – the owner of the instant application); Nimish Vakil, M.D. (a practicing physician whose Declaration has been filed in this instant application); Primary Examiner Dameron Jones; and the undersigned attorney.

During the interview, amendments were discussed to clarify the claims in view of possible 35 U.S.C. § 112 (¶¶ 1 and 2) rejections. Claims 49; 87; 88; 89; 90; 94; 96; 97; 105; 107; 110; 116; and 117 have been amended consistent with these discussions. Claim 93 has been cancelled in light of the amendment to claim 49. Claims 50 to 86 were previously cancelled.

Claims 49; 87 to 92; and 94 to 117 remain in the application. Of these, claim 49 is the sole independent method claim.

The Examiner requested that support for the terminology “an alkaline-reacting substance admixed with the PPI” found in claims 95; 99; 106; and 109 be identified in the Specification. Support for this terminology is found on Specification page 11, lines 16-17; Specification page 20, line 29; and Specification page 22, lines 16-17.

The Examiner also requested evidence that a person of ordinary skill in the art would understand the terminology “isomers (of PPI) including enantiomers” and “isomers (of H₂RA)” found in claim 49 (as amended) (for which support appears on Specification page 9, lines 27-33). Applicant attaches excerpts from Hawley's Condensed Chemical Dictionary (13th Edition) (1997), where the definitions for “enantiomer” and “isomer” appear. Both are well known terms of art in the field of organic/medicinal chemistry, and a person of ordinary skill in the art to which the invention pertains would readily understand their meaning in the context of the claims.

During the Interview, Nimish Vakil, M.D., addressed the level of ordinary skill in the art to which the invention pertains at the time the invention was made. Dr. Vakil's opinions in this regard are more fully set forth in his Declaration. With the aid of Figures 1 to 7 contained in his Declaration, Dr. Vakil discussed the physiologic mechanism by which acid is secreted in the human stomach. With the aid of Figures 8 and 9 contained in his Declaration, Dr. Vakil explained the mechanism of acid secretion inhibition caused by the antisecretory drug H₂RA, as well as the

different mechanism of acid secretion inhibition caused by the antiseoretory drug PPI, as understood by a person of skill in the art at the time the invention was made. From the perspective of a person of ordinary skill in the art, Dr. Vakil explained the prejudice that existed at the time the invention was made that warned against the concurrent or simultaneous administration of a H2RA and PPI to a human. From the perspective of a person of ordinary skill in the art at the time the invention arose, and referring to peer literature at the time (*Sleisenger and Fortran* 5th Edition, 1993, p. 626-627) (*Sleisenger and Fortran* 6th Edition, 1998, p. 648-649) (*Wolfe et al*, *Gastroenterology*, 2000, p. S14), Dr. Vakil demonstrated the magnitude of the prejudice against concurrent or simultaneous administration of a H2RA and PPI to a human that existed at that time. Dr. Vakil reviewed the dog data (*De Graef et al*, *Gastroenterology*, 1986, p. 335-336) that scientifically supported the prejudice at the time. Dr. Vakil then reviewed the clinical data (*Fändriks et al*, *Scandinavian Journal* 2007, p. 693) that demonstrates the surprising clinical result that the invention defined in the claims provides.

Also during the Interview, with the aid of Figure 10 contained in his Declaration, Dr. Vakil discussed the significant pharmacological difference between antisecretory drugs (such as PPI and H2RA) and the acid neutralizing drugs called antacids. Dr. Vakil referred to United States Patent No. 5,229,137 for Dr. Wolfe's invention of the concurrent administration of H2RA and antacid. Dr. Vakil noted that Dr. Wolfe is the same individual (see *supra Wolfe et al*, *Gastroenterology*, 2000, p. S14) who expressed in no uncertain terms the magnitude of the prior art prejudice against the instant invention: "(PPI's) should *not* be used in conjunction with H₂-receptor antagonists, postaglandins, or other antisecretory agents."

During the Interview, applicant addressed the rejections of the claims in the instant application based upon Saslawski (WO 99/33448) During the interview, applicant also addressed the prior art rejections in the related co-pending applications Serial No. 10/475,254 and Serial No. 11/822,502 (the "Related Applications") based upon Coffin (WO 95/22320) and McGrew (US 6,949,264). Copies of the Examiner's office actions in the Related Applications have been previously submitted to the Examiner in the instant application.

Applicant believes that the record establishes that, taking into account the scope and content of the prior art, the differences between the claim invention and the prior art, and the level of ordinary skill in the art, the subject matter defined in amended claims 49; 87 to 92; and 94 to 117 is not encompassed by the prior art.

At the conclusion of the Interview, the Examiner indicated that agreement was reached with respect to the claims, further writing: "Applicant presented the state of the art outlined in the Declaration submitted. The Examiners made suggestion to clarify the claims and overcome possible 112 1st or 2nd rejections. Applicant will file the amendments while the Examiner considers the Declaration. The Examiner will contact Applicant for any other possible rejections (112 or otherwise)." The amendments presented are believed to comply with the Examiner's suggestions, and the applicant is committed to proceed expeditiously by telephone as discussed during the Interview.

The Examiner's attention is directed to the Supplemental Information Disclosure Statement that accompanies this Amendment. The Statement lists the article -- De Gaaef et al, "Influence of the Stimulation State of the Parietal Cells on the Inhibitory Effect of Omeprazole on Gastric Acid Secretion in Dogs," *Gastroenterology* 1986:91:333-7 -- which was discussed during the Interview (the "dog data"). A copy of the article also accompanies the Statement.

As expressed during the Interview, if the Examiner believes that the amended claims are allowable, but for non-statutory obviousness-type double patenting in view of the amended claims presented in related application Serial No. 11/544,750, which were also addressed during the Interview, applicant will expeditiously submit a Terminal Disclaimer to overcome the double patenting rejection. Applicant believes that such matters can be handled expeditiously by an interview by telephone to advance prosecution.

As also expressed during the Interview, if the Examiner believes that other questions or other matters of clarification remain, applicant believes that such matters also can be handled expeditiously by an interview by telephone to advance prosecution of this case, and the applicant is committed to proceed on that basis.

Respectfully Submitted,

By


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Hawley's
Condensed Chemical
Dictionary

THIRTEENTH EDITION

Revised by
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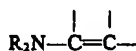
en. Abbreviation for ethylenediamine, used in formulas for coordination compounds, e.g., the cobalt complex $\text{Co}[\text{en}]_3(\text{NO}_3)_3$.
See dien; pn; py.

enamel. (1) A type of paint consisting of an intimate dispersion of pigments in a varnish or resin vehicle. The vehicle may be an oil-resin mix or entirely synthetic resin. Those containing drying oils are converted to films by oxidation; those composed wholly of synthetic resins may be converted by either heat or oxidation, or both.

See baking finish.

(2) Porcelain enamel.

enamine. A group of amino olefins; the name refers especially to unsaturated tertiary amines of the general formula



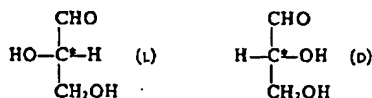
where R is any alkyl group. Though of little use as end products, enamines are valuable intermediates for many organic syntheses.

enanthaldehyde. See heptanal.

enanthic acid. See *n*-heptanoic acid.

enanthyl alcohol. See heptyl alcohol.

enantiomer. (enantiomorph). One of a pair of optical isomers containing one or more asymmetric carbon atoms C^* whose molecular configurations have left- and right-hand (chiral) forms. These forms are conventionally designated dextro (D) and levo (L) because they compare to each other structurally as do the right and left hands when the carbon atoms are lined up vertically. This is apparent in the enantiomorphs of glyceraldehyde; the two structures are mirror images of each other and cannot be made to coincide:



Several pairs of enantiomers are possible, depending on the number of asymmetric carbon atoms in the molecule. Compounds in which an asymmetric carbon is present display optical rotation.

See asymmetry; optical isomer; optical rotation.

enantiomorph. See enantiomer.

encapsulation. The process in which a material or an assembly of small, discrete units is coated with or imbedded in a molten film, sheath, or foam, usually of an elastomer. A foam-forming plastic

may be used to fill the spaces between various electrical or electronic components so that they are imbedded in and supported by the foam. Plastics and other materials used for this purpose are often called potting compounds. A specialized use of this technique is in growing crystals for semiconductors, in which a coating of liquid boric oxide is the encapsulating agent. Use of a glassy silicate coating to encapsulate nuclear waste for permanent disposal is under investigation.

See microencapsulation.

"Endic" anhydride [Velsicol]. TM for *endo-cis*-bicyclo(2.2.1)-5-heptene-2,3-dicarboxylic anhydride. ($\text{C}_8\text{H}_8\text{O}_3$).

Properties: White crystals. Mp 163°C. Soluble in aromatic hydrocarbons, acetone, ethanol.

Use: Elastomers, plasticizers, fire retardant chemicals, resins, and epoxy curing systems.

endo-. A prefix used in chemical names to indicate an inner position, specifically (1) in a ring rather than a side chain or (2) attached as a bridge within a ring.

See *exo*-.

endomycin. An antifungal antibiotic complex produced by streptomycetes.

"Endor" [Du Pont]. TM for a rubber peptizing agent containing activated zinc salt of pentachlorothiophenol. ($\text{C}_6\text{Cl}_5\text{S}$)₂Zn and 80% inert filler.

Properties: Grayish-green powder. D 2.39.

endorphin. Any of a group of polypeptides formed in the brain tissue and pituitary gland of higher animals that are thought to control the transfer of signals at nerve junctions, thus ensuring that behavior patterns in the individual remain normal. Imbalance or malfunction of these polypeptides has been reported to be a factor in irrational and violent actions and other emotional disorders, as well as in epilepsy and memory processes. This belongs to a developing field of medicinal chemistry called neuropharmacology.

endosmosis. The passing of a fluid inward through a porous partition toward another fluid of different character.

See exosmosis; Perrin rule.

endosulfan. (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide).

CAS: 115-29-7. $\text{C}_6\text{H}_2\text{Cl}_6\text{O}_3\text{S}$.

Properties: (commercial product): Brown crystals. Mp 70–100°C (pure: mp 106°C). Mixture of two isomers. Mp 108–109°C and 206–208°C.

Hazard: Toxic by ingestion, inhalation, and skin absorption; use may be restricted. TLV: 0.1 mg/m³ of air.

Use: Insecticide.

Grade: Perfumer's grade, FCC.

Use: Perfumes, vanillin, flavoring agent.

isoeugenol acetate. See acetylisoegenol.

isoeugenol ethyl ether. (1-ethoxy-2-methoxy-4-propenyl-benzene). $C_3H_5(CH_3O)C_6H_4OC_2H_5$.

Properties: Synthetic, white, crystalline powder. Mp 64C. Insoluble in water; soluble in alcohol, ether, benzene. Combustible.

Use: Sweetening agent and odorant fixative.

isofluorophate. See diisopropyl fluorophosphate.

"Isoforming." Proprietary process for fixed-bed hydroisomerization, requiring a non-noble-metal catalyst. Claimed to give high yields of C_8 (xylene) isomers with low hydrogen consumption and minimal catalyst regeneration.

isoheptane. See 2-methylhexane.

isohexane.

CAS: 107-83-5. C_6H_{14} . A mixture of branched-chain isomers.

Properties: Colorless liquid. Boiling range 54-61C, d 0.671 (15.5/15.5C), flash p -26F (-32C) (CC).

Grade: Commercial.

Hazard: Highly flammable, dangerous fire and explosion risk, explosive limits in air 1-7%.

Use: Solvent, freezing-point depressant.

isolan. See 1-isopropyl-3-methyl-5-pyrazolyl dimethylcarbamate.

isolated double bond. Double bond separated by more than one single bond linkage from the next double bond.

isolation. Identification and separation of a pure substance that is present in trace amounts in a complex mixture. A famous instance of this was the isolation of polonium (1898) and radium (1912) from pitchblende by the Curies by coprecipitation techniques followed by repeated fractional crystallization.

isoleucine. (2-amino-3-methylpentanoic acid; Ile).

CAS: 73-32-5. $CH_3CH_2CH(CH_3)CH(NH_2)COOH$. An essential amino acid, found naturally in the L(+) form.

Properties: Crystals. Slightly soluble in water; nearly insoluble in alcohol; insoluble in ether.

Derivation: Hydrolysis of protein (zein, edestin), amination of α -bromo- β -methylvaleric acid.

Use: Medicine, nutrition, biochemical research.

"Isomate" [Upjohn]. TM for isocyanate foam systems. Available as nonburning, pour-in-place froth, or spray foams.

isomer. (1) One of two or more molecules having the same number and kind of atoms and hence the same molecular weight, but differing in respect to the arrangement or configuration of the atoms. Butanol (C_4H_9OH or $C_4H_{10}O$) and ethyl ether

($C_2H_5OC_2H_5$ or $C_4H_{10}O$) have the same empirical formulas but are entirely different kinds of substances; normal butanol ($CH_3CH_2CH_2CH_2OH$) and isobutanol ($[(CH_3)_2CHCH_2OH]$) are the same kinds of substances, differing chiefly in the shape of the molecules; *sec*-butanol ($CH_3CH_2OCH_2CH_3$) exists in two forms, one a mirror image of the other (enantiomer). Isomers often result from location of an atom or group of a compound at various positions on a benzene ring, e.g., xylene, dichlorobenzene.

(2) Nuclides (i.e. kinds of atomic nuclei) having the same atomic and mass numbers, but existing in different energy states. One is always unstable with respect to the other, or both may be unstable with respect to a third. In the latter instance the energy of transformation in the two cases will differ. See geometric isomer; optical isomer.

isomerization. A method used in petroleum refining to convert straight-chain to branched-chain hydrocarbons, or alicyclic to aromatic hydrocarbons, to increase their suitability for high-octane motor fuels. For example, butane (a gaseous paraffin hydrocarbon, $CH_3CH_2CH_2CH_3$) can be slightly modified in structure by catalytic reactions to give the isomeric isobutane ($CH_3CH_2CHCH_3$) used as a component of aviation fuel. Similarly, methylcyclopentane can be isomerized to cyclohexane, which is then dehydrogenated to benzene. Isomerization techniques were introduced on a large scale during World War II.

See isomer; chain.

α -isomethylionone. (γ -methylionone). $C_{14}H_{22}O$. Properties: Slightly yellow liquid. D 0.925-0.929 (25/25C), refr index 1.5000-1.5010 (20C), flash p 217F (102.7C) (TCC). Soluble in 5 parts of 70% alcohol. A synthetic product. Combustible. Use: Floral perfumes, particularly of a violet character; flavoring.

isomorphism. The state in which two or more compounds that form crystals of similar shape have similar chemical properties and can usually be represented by analogous formulas, e.g., Ag_2S and Cu_2S .

isonipocaine hydrochloride. See meperidine hydrochloride.

isonitrile. See carbylamine.

"Isonol C100" [Upjohn].

$C_8H_9N[CH_2CH(CH_3)OH]_2$. An aromatic reinforcing polyol.

Properties: Amber liquid. Viscosity (50C) 1000 cP (max), d 1.055 (23C), water content 0.05%. Combustible.

Use: Ingredient of polyurethane foams, coatings, sealants, and elastomers; intermediate in organic synthesis.